## Cosmetic outcome and patient satisfaction

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# Chapter 6

## Neoadjuvant chemotherapy in breast-conserving surgery – Consequences on margin status and excision volumes: A nationwide pathology study

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# Abstract


## Background

Neoadjuvant chemotherapy (NACT) is increasingly used in patients with operable disease due to the potential of converting patients requiring mastectomy to breast conserving surgery (BCS) or lowering resection volumes to improve cosmetic outcome. This nationwide retrospective study aims to determine margin status and specimen volume in patients with invasive breast cancer who underwent BCS after NACT.

## Methods

All patients who underwent BCS in 2012–2013 for invasive breast cancer were selected from a nationwide network and registry of histology and cytopathology in the Netherlands (PALGA).

## Results

Of the 9901 patients, 626 (6.3%) received NACT. After primary surgery 949 (10.2%) patients had tumor-involved margins compared to 152 (24.3%) after NACT. Close margins (≤1 mm) were seen in another 111 (17.7%) patients after NACT. The adjusted odds ratio for involved margins after NACT was 2.94, meaning a three times higher risk of involved margins compared with primary surgery. In patients with lobular carcinoma (54.9%) and no response to NACT (42.1%) higher tumor-involved margins were seen. High resection volumes >60 cc were observed in 224 (36%) patients after NACT of which 37 (16.5%) had tumor involved margins and 32 (14.3%) close margins ≤1 mm.

## Conclusion

The primary goal of the surgeon performing BCS after NACT, to reach tumor-free margins, is not accomplished in one out of four patients. Patients especially at risk are patients with ILC and no pathological tumor response. Excessive resection volumes after NACT do not guarantee tumor-free margins. Further research is necessary to analyze whether we are counterproductive when NACT is given in order to lower resection volumes.

# Introduction

Neoadjuvant chemotherapy (NACT) is increasingly used in breast cancer patients who have an indication for systemic chemotherapy at the time of presentation, to lower resection volumes in patients with large tumor sizes as well as to convert patients to be candidates for breast conserving surgery (BCS) who would otherwise be candidates for mastectomy.[1–6] Additionally, NACT can eradicate (micro)metastatic disease in the regional lymph nodes, sometimes changing the treatment strategy of the axilla.[4,5,7] An early evaluation of the effectiveness of NACT can be assessed and, in non-responders, ineffective treatment can be discontinued. However, patients after NACT do not seem to benefit in terms of overall survival (OS) and progression free survival (PGS) when compared patients who received chemotherapy in the adjuvant setting.[1,2,8–11]

The primary goal of BCS is to achieve tumor-free margins as tumor-involved margins have a higher risk of locoregional recurrence (LRR). Therefore, in order to prevent LRR, additional treatment such as a radiotherapy boost, re-excision or even mastectomy is advocated in case of tumor-involved margins.[12] Tumor-involved margins up to 24.7% after NACT are reported.[3,11,13–19]

A secondary goal after BCS is achieving a satisfactory cosmetic outcome. The key determinant of cosmetic outcome has shown to be the volume of healthy breast tissue resected and fair or poor cosmetic outcomes are observed in up to 37% of all patients after BCS.[20–27]

The present retrospective study aims to assess margin status and lumpectomy volume of all patients treated with BCS after NACT in the Netherlands in 2012–2013 in order to improve indications for BCS after NACT.

# Methods

**Patient selection**

All women with primary invasive breast cancer who underwent BCS with or without NACT in 2012–2013 were registered in the Dutch Pathology Registry (PALGA, the nationwide network and registry of histo-and cytopathology in the Netherlands).[28] This resulted in the analysis of 9901 anonymized pathology reports including core biopsy, excision specimen and re-excision or mastectomy after BCS for the same patient. These unique excerpts could not be traced back to the hospital in which BCS was performed. Therefore, despite their relevance, extracting clinical data was impossible due to anonymization of the pathological data. Encryption of the patient identifiers ensures the patients privacy.

**Breast cancer pathology excerpts**

For pathological processing and reporting of breast specimens national uniform guidelines exist. According to the Dutch Breast Cancer Guideline, the pathology report should include: histological tumor type, greatest tumor diameter for invasive and in situ carcinoma, tumor grade, oestrogen-, progesterone- and HER2-receptor status, closest margin width or involvement for invasive and in situ carcinoma and which margin it concerns. For patients after NACT, the response to pre-treatment according to The European Society Of Breast Cancer Specialists (EUSOMA) and maximum diameter of the fibrotic area must be reported.[12] In core biopsy before NACT, histological type according to WHO, grade, oestrogen-, progesterone- and HER2-receptor status must be reported. Additionally, excision method, gender and age were provided by PALGA.

**Patient and tumor-characteristics**

The two main histological tumor types were distinguished: invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC). Other tumor types were grouped together in the group called "other". Five excision methods were initially defined but we chose to group them as 'excision without localization' (standard lumpectomy, wide local excision and segmentectomy), wire-guided excision and iodine-125 guided excision. Ultrasound-guided surgery and radio occult lesion localization (ROLL) were not described in pathology excerpts. Molecular subtypes of patients in the primary surgery group were based on excision specimen, in the NACT group these data were based on the pre-operative biopsies because molecular subtype can change due to neoadjuvant chemotherapy.

Response to NACT was classified according to EUSOMA criteria.

1: complete pathological response.
2: partial response.
   (i) minimal residual disease/near total effect.
   (ii) 10–50% tumor remaining.
   (iii) >50% tumor cellularity remains evident.
3: no evidence of response to therapy.

Tumor diameter was considered unreliable because some pathologist only described fibrotic area, even in patients with partial response. Therefore a calculated resection ratio, indicating the amount of healthy breast tissue resected, could not be defined in the present study.

### Margin status definition

According to Dutch National guidelines, a tumor-free margin is defined as the absence of tumor cells at the inked margins. When unexpected DCIS was found at the margin during pathological examination this was also reported. Furthermore, close margins were defined as tumor cells ≤1 mm from the nearest margin.

### Calculation of the volumes

Data provided by PALGA provided lumpectomy weight or measurements in three dimensions (length, width and height). When weight was provided, it was used as the volume, as weight and volume of lumpectomy specimens are almost equal.[29] When weight was not provided, volume was calculated using the three dimensions of the specimen and the formula for an ellipsoid (4/3π (length×width×height)).

### Statistical analyses

Data were analyzed using the Statistical Package for the Social Sciences (SPSS, Version 21.0; IBM). Patient and tumor characteristics were compared between NACT and primary surgery using Mann–Whitney and chi-square tests. Tumor-free margins were compared to involved margins using Mann–Whitney, Fisher's exact, Chi-square or linear-by-linear tests and lumpectomy volume was compared between different response statuses using Jonckheere Terpstra test. Logistic regression was performed to compare odds of having involved margins to free margins and to identify risk factors for margin status. The regression model could not be applied to investigate risk factors among NACT patients due to sample size issue. The results were considered significant at a 5% significance level.

## Results

### Patient and tumor characteristics (Table 1)

Of the 9902 patients, 626 (6.3%) received NACT. Median age was 62 (24–97) years in the group without NACT and 53 (24–94) years in the neoadjuvant group. A slightly higher percentage of ILC was found in the neoadjuvant group compared to the BCS group without NACT (11.3% vs 9.0%). After NACT, more often I-125 seed localization was used (4.8 vs 1.4%, p = 0.001). In 646 patients (6.5%) hormonal receptor status and in 923 patients (9.3%) Her2neu receptor status was missing. In the neoadjuvant group more hormonal negative (14.6% vs 11.9%, p = 0.085) and less Her2neu negative tumors (84.6% vs 91.4%, p=<0.001) were seen. There was no significant difference in triple negative tumors between the group without NACT and the neoadjuvant group, respectively 9.7% versus 11.7%.

**Margin status (Table 1)**

Involved margins in the BCS group without NACT were reported in 10.2% of patients. Involved margins including DCIS were seen in 16.4%. Close margins for invasive carcinoma (defined as tumor cells ≤1 mm of the margin) occurred in another 1618 lumpectomies (17.4%). Involved margins in the neoadjuvant group were 24.3%, which is higher compared to the primary surgery group. Involved margins including DCIS in the neoadjuvant group were also significantly higher and were seen in 27.3%. Close margins for invasive carcinoma (≤1 mm) were seen in another 111 (17.7%) patients.

Neoadjuvant chemotherapy resulted in significantly higher odds of having tumor-involved margins when compared to BCS only (Table 2). The unadjusted odds ratio was 2.81 (95%CI 2.31–3.42) and adjusted odds ratio for age, histopathological type, hormonal receptor status, her2neu status, triple negative status, excision method, and lumpectomy volume was 2.87 (95%CI 2.23–3.68).

No differences in margin status between excision methods in the NACT group were seen ($p = 0.693$). In patients with lobular carcinoma (54.9%), patients who are not triple negative (25.8%) and patients with positive hormonal (26.1%) or negative Her2neu receptor status (25.5%) a higher amount of tumor-involved margins were reported (Table 3).

**Table 1.** Patient and tumor characteristics for primary surgery and neoadjuvant systemic therapy after breast conserving surgery therapy after breast conserving surgery.

| | **Primary surgery (N = 9275)** | **NACT (N = 626)** | **Total (N = 9901)** | **p-value** |
|---|---|---|---|---|
| **Age in years** (median, range) | 62 (24–97) | 53 (24–94) | 61 (24–97) | <0.001[a] |
| **Histopathological type** | | | | 0.001[b] |
| Invasive ductal carcinoma | 7780 (83.9%) | 532 (85.0%) | 8312 (84.0%) | |
| Invasive lobular carcinoma | 832 (9.0%) | 71 (11.3%) | 903 (9.1%) | |
| Other | 663 (7.1%) | 23 (3.7%) | 687 (6.9%) | |
| **Localization method** | | | | <0.001[b] |
| Palpation guided | 6784 (73.1%) | 462 (73.8%) | 7246 (73.2%) | |
| Wire guided | 2360 (25.4%) | 134 (21.4%) | 2494 (25.2%) | |
| I-125 guided | 131 (1.4%) | 30 (4.8%) | 161 (1.6%) | |
| **Hormonal status*** | | | | 0.085[b] |
| Positive | 7742 (88.1%) | 399 (85.4%) | 8141 (88.0%) | |
| Negative | 1046 (11.9%) | 68 (14.6%) | 1114 (12.0%) | |
| **Her2neu status*** | | | | <0.001[b] |
| Positive | 732 (8.6%) | 66 (15.4%) | 798 (8.9%) | |
| Negative | 7818 (91.4%) | 362 (84.6%) | 8180 (91.1%) | |
| **Triple negative*** | | | | 0.16[b] |
| Yes | 856 (9.7%) | 55 (11.7%) | 911 (9.8%) | |
| No | 7928 (90.3% | 415 (88.3%) | 8343 (90.2%) | |
| **Margins for invasive carcinoma** | | | | <0.001[b] |
| Tumor free margins | 8326 (89.8%) | 474 (75.7%) | 8800 (88.9%) | |
| Tumor involved margins | 949 (10.2%) | 152 (24.3%) | 1101 (11.1%) | |
| **Margins for invasive carcinoma and DCIS** | 7756 (83.6%) | 455 (72.7%) | 8211 (82.9%) | <0.001[b] |
| Tumor free margins | 1519 (16.4%) | 171 (27.3%) | 1690 (17.1%) | |
| Tumor involved margins | | | | |
| **Close margins** | | | | |
| Invasive margins ≤1 mm | 1618 (17.4%) | 111 (17.7%) | 1729 (17.5%) | <0.001[b] |
| Invasive margins >1 mm | 6639 (71.6%) | 341 (74.1%) | 6990 (70.6%) | |
| Unknown | 70 (0.8%) | 11 (1.8%) | 81 (0.8%) | |
| **Lumpectomy volume** (median, range) | 46 (1–807) | 50 (5–679) | 46 (1–807) | 0.14[a] |

* For NACT, hormonal and her2neu receptor status was determined on needle biopsy pre-chemotherapy.

[a]Mann–Whitney, [b]Chi square.

Table 2. Odds ratios of margin status for invasive carcinoma.

| | Univariate model | | Multivariate model | |
|---|---|---|---|---|
| | **OR (95% CI)** | **p-Value** | **OR (95% CI)** | **p-Value** |
| **Neoadjuvant therapy** | | | | |
| No | 1 (Ref) | <0.01 | 1 (Ref) | <0.01 |
| Yes | 2.81 (2.31–3.42) | | 2.87 (2.23–3.68) | |
| **Age** (per 5 years) | 0.96 (0.94–0.99) | 0.011 | 0.97 (0.94–1.00) | 0.09 |
| **Histopathological type** | | | | |
| Invasive ductal carcinoma | 1 (Ref) | <0.01 | 1 (Ref) | <0.01 |
| Invasive lobular carcinoma | 3.07 (2.60–3.63) | 0.12 | 3.46 (2.45–4.91) | 0.33 |
| Other | 0.80 (0.60–1.06) | | 1.167 (0.86–1.60) | |
| **Excision method** | | | | |
| Without localization | 1 (Ref) | 0.44 | 1 (Ref) | 0.43 |
| Wire guided | 0.86 (0.74–1.0) | 0.27 | 0.94 (0.80–1.10) | 0.11 |
| I-125 guided | 0.73 (0.42–1.27) | | .62 (0.34–1.11) | |
| **Lumpectomy volume (per 10 cc)** | 0.98 (0.96–0.99) | <0.01 | 0.97 (0.96–0.99) | <0.01 |
| **Hormonal status** | | | | |
| Positive | 1 (Ref) | <0.01 | 1 (Ref) | 0.81 |
| Negative | 1.59 (1.26–2.01) | | 1.07 (0.64–1.79) | |
| **Her2neu status** | | | | |
| Positive | 1 (Ref) | 0.38 | 1 (Ref) | 0.44 |
| Negative | 0.90 (0.70–1.14) | | 1.12 (0.85–1.48) | |
| **Triple negative** | | | | |
| Yes | 1 (Ref) | <0.01 | 1 (Ref) | 0.24 |
| No | 0.60 (0.46–0.78) | | 0.71 (0.40–1.25) | |

Table 3.Patient and tumor characteristics of BCS after NACT considering margins status of invasive carcinoma

| | Tumor-free margins | Tumor-involved margins | p-value |
|---|---|---|---|
| **Total** | 474 (75.7%) | 152 (24.3%) | |
| **Age in years**(median) | 53 (24-94) | 52 (27-92) | 0.903[a] |
| **Histopathological type** | | | |
| Invasive ductal carcinoma | 423 (79.5%) | 109 (20.5%) | <0.001[b] |
| Invasive lobular carcinoma | 32 (45.1%) | 39 (54.9%) | |
| Other | 19 (82.6%) | 4 (17.4%) | |
| **Excision method** | | | |
| No localization | 346 (74.9%) | 80 (25.1%) | |
| Wire guided | 104(77.6%) | 30 (22.4%) | 0.693[b] |
| I-125 guided | 24 (80.0%) | 6 (20.0%) | |
| **Response** | | | |
| (near)complete response(1+2i) | 81 (88.0%) | 11 (12.0%) | <0.001[d] |
| Partial response(2ii + 2iii) | 305 (74.4%) | 105 (25.6%) | |
| No response(3) | 22 (57.9%) | 16 (42.1%) | |
| **Hormonal status** | | | |
| Positive | 295 (73.9%) | 104 (26.1%) | 0.001[c] |
| Negative | 64 (94.1%) | 4 (5.9%) | |
| **Her2neu status** | | | 0.011[c] |
| Positive | 57 (86.4%) | 3 (13.6%) | |
| Negative | 271 (74.5%) | 97 (25.5%) | |
| **Triple negative** | | | |
| Yes | 53 (96.4%) | 2 (3.6%) | <0.001[c] |
| No | 308 (74.2%) | 107 (25.8%) | |
| **Lumpectomy volume in cc** (median) | 52 (5-679) | 39 (6-250) | <0.001[a] |

[a]Mann Whitney [b]Fisher exact test, [c]Chi Square test,[d]Linear by linear test.

Response according to EUSOMA was reported in 540 (86%) patients. Of the patients with no tumor response, 42.1% had tumor involved margins compared with 25.6% of patients with partial response and 12.0% of patients with a (near) complete response ($p < 0.001$).

## Additional surgical therapy (Table 4)

Patients after NACT received more additional surgical therapy (9.1%) compared to patients after BCS without NACT (5.3%, $p < 0.001$). After NACT, in 4.0% a re-excision was performed and 4.9% eventually ended up with a mastectomy.

Table 4. Additional surgical therapy, residual tumor and margin status.

| | Primary surgery (N=9275) | NACT (N=626) | Total (N=9901) | p-value |
|---|---|---|---|---|
| **Additional surgical therapy** | | | | <0.001[a] |
| Yes | 493 (5.3%) | 57 (9.1%) | 550 (5.6%) | |
| No | 8782 (94.7%) | 569 (90.9%) | 9351 (94.4%) | |
| **Type of additional therapy** | | | | <0.001[a] |
| Re-excision | 217 (2.3%) | 25 (4.0%) | 242 (2.4%) | |
| Mastectomy | 258 (2.8%) | 29 (4.6%) | 287 (2.9%) | |
| Mastectomy after re-excision | 17 (0.2%) | 2 (0.3%) | 19 (0.2%) | |
| Second re-excision | 1 (0.01%) | 1 (0.2%) | 2 (0.02%) | |
| **Additional tumor in specimen** | | | | 0.001[a] |
| None | 178 (35.8%) | 21 (36.8%) | 199 (35.9%) | |
| DCIS | 157 (31.5%) | 6 (10.5%) | 163 (29.4%) | |
| Invasive carcinoma | 163 (32.7 %) | 30 (53.6%) | 193 (34.8%) | |
| **Margin status in patients with residual invasive carcinoma after re-excision.** | | | | 0.603[a] |
| Tumor-free margins | 135 (82.8%) | 26 (86.7%) | 166 (86.0%) | |
| Tumor-involved margins | 28 (17.2%) | 4 (13.3%) | 32 (14.0%) | |
| **Margin status in patients with residual invasive carcinoma or DCIS after re-excision*** | | | | 0.527[a] |
| Tumor-free margins | 272 (85.0%) | 32 (88.9%) | 304 (85.4%) | |
| Tumor-involved margins | 48 (15.0%) | 4 (11.1%) | 52 (14.6%) | |

[a]=chi square.

# Discussion

While historically NACT was limited to patients with locally advanced breast cancer, nowadays it is frequently administered to women with operable breast cancer in an effort to lower resection volumes and avoid mastectomy or extensive axillary surgery.[1–7] Still, the primary goal of BCS after NACT is to resect any residual tumor with tumor-free margins. The current study reports that surgeons do not succeed in reaching this goal in 24.3% of patients. Although considered as tumor-free margins, another 17.7% had close margins, which can be an indication for re-excision after BCS (with or without NACT) in a number of countries. For instance Danish National Guidelines recommend tumor-free margins ≤2 mm.[30] Amongst others, Germany and France have BCS guidelines on margin status which indicate that patients with margins ≤1 mm should undergo additional surgery.[31,32] Despite these guidelines, substantial surgeon and institutional variations are observed in performing re-excisions after BCS.[33] Patients treated with NACT are excluded in international guidelines and no guideline or margin status definition is available considering these patients.[12]

This study reports similar tumor-involved margin rates of BCS after NACT compared to other studies.[13–18] In a retrospective single center study, Fukutomi et al. reported 28/113 (24.7%) patients with tumor-involved margins (46% invasive, 54% non-invasive component).[16] By performing intra-operative margin assessment, Peintinger et al. showed improved results by performing re-resections intra-operatively in case of tumor-involved margins, leading to 16% involved-margins.[14] However, comparison of studies remains difficult, as different patient populations and different definitions of margin status (with or without DCIS) are used. More important, due to differences in patient and tumor characteristics, patients after NACT cannot solely be compared to patients treated without NACT.

Our study reports a higher tumor-involved margin rate in patients with ILC compared to IDC after NACT. Similar results have been reported and can be explained by the distinctive, branch-like *growth pattern and* lower pathologic complete response rates in ILC.[3,32]

The use of NACT in patients with T3 tumors resulted in an increase in BCS from 3% to 22% (margin status unknown).[4,34] Considering the high rate of tumor-involved margins after NACT, it is necessary to analyze whether we are counterproductive in some patients undergoing NACT when given for downstaging of the tumor.

There is no consensus on performing additional therapy (boost, re-excision or mastectomy) in case of 'tumor-involved margins' in BCS after NACT. In this study, overall 5.6% of the patients underwent additional surgical therapy which is much lower than reported in recent literature.[33,35] We do not know how the other patients with tumor-involved margins have been treated, it is possible that they have received additional radiotherapy. We also expect that the amount of secondary surgery in this database is an underestimation. However, it is

striking that again 13–17% show involved margins after secondary surgery for close or involved margins.

Varying numbers of additional therapy are reported, with up to 27% of patients undergoing a re-excision after NACT.[11,13–17,19,36] Whether these additional therapies influence LRR is not yet clear. Tumor biology and disease stage may also play an important role in LRR after NACT. Unfortunately, no data are available from prospective trials regarding LRR in relation to margin status or additional therapy and retrospective studies show varying results.[1,2,8,9,11,19,34] Despite the difference in definitions and patient populations between studies, it is clear that re-excision rates after NACT seem to be unacceptably high, especially considering the negative influence of additional local treatments on cosmetic outcome, psychological distress and medical costs.[20,23,35]

When NACT started to be given for downstaging of large tumors to lower resection volumes, the area of concern was the possible increase in LRR when a tumor does not shrink into a solitary residual disease. Patients with solitary lesions after chemotherapy are considered suitable for BCS, whereas the ones with multifocal and patch like residual lesions require extra caution.[37,38] Intraoperative frozen biopsies might miss satellite lesions due to selective assessment of the 5 mm slides and this could lead to LRR.[14,39]

In this perspective, Morrow et al. advised that if viable tumor is present throughout the specimen, even if it does not extend to the margin, a further re-excision should be considered.[38]

Achievement of pathological complete response (pCR) is a powerful prognostic predictor of long-term outcome, with significantly better disease-free and overall survival compared with patients having residual tumor.[37] In our study, patients with a near complete response (EUSOMA 1 and 2i) had lower tumor-involved margins (12.0%) compared to patients with no tumor response (42.1%), possibly improving oncological outcome.

Patients with Her2neu positive and triple negative tumors are known to show high pCR rates.[2,40] This is possibly reflected in the low amount of tumor-involved margins in these patients in our study. However, it must be realized that hormonal and her2neu receptor-status can change in 8–33% after NACT.[40] Considering the ongoing debate on the confounders in changing of biomarkers and the future perspectives on tailored (neo)adjuvant therapies, receptor status was included in this study.

NACT has the potential for improving the cosmetic outcome by reducing the amount of breast tissue that must be removed, even in patients who are already candidates for breast-conserving surgery.[4,5] No study describes cosmetic outcome in patients treated with BCS after NACT for this purpose. In this study more than one third of the patients had a volume above 60 cc. Unfortunately, pre-operative tumor diameter could not be analyzed, which is important when interpreting these results. However, cosmetic failure has been described to be significantly higher if the size of the lump exceeds 40–50 cc.[23,26]

It is striking that when a (near) complete pathologic response after NACT was observed, patients underwent larger lumpectomy volumes. Another retrospective study in 109 patients with pCR showed also large volumes of 73 cc.[36] A high tumor response after NACT was originally thought to reduce large tumors into a size that is eligible for BCS. However, high response is generating a new problem: difficulty in determine the borders of resection perioperatively. The challenge for surgeons after NACT is localizing a (non-palpable) lesion with resection of the minimum amount of healthy tissue while achieving tumor-free margins. Large volumes after pCR could be explained by performing 'blind' surgery. To utilize imaging of the original location after NACT, in most centres a radiopaque marker is placed before NACT. In addition, at the completion of chemotherapy MRI and USS are frequently used to evaluate pathological response and to assess the location and extent of the residual tumor.[4,5,12] Despite these measures of visualizing the tumor-site, still a high rate of tumor-involved margins after NACT is reported. It is therefore desirable to improve our knowledge on the clinical and pathological response pre-operatively to identify patients with a pCR or high risk patients with no response to NACT and to improve visualization of (residual) tumor perioperatively to obtain a higher rate of free margins, decrease healthy breast tissue resection and improve of cosmetic outcome.

The M.D. Anderson prognostic index was developed for selecting patients for breast BCT after NACT on the basis of their risk of developing local failure. Factors predictive of increased local failure rates were clinical N2 or N3 disease, residual tumor size >2 cm, a multifocal pattern of residual disease and lymphovascular space invasion. The percentage of patients with positive surgical margins was too low (4%) to be analyzed as a prognostic factor. Unfortunately, most factors can be determined only after surgery and are therefore not available for surgical procedure planning, something which will hopefully can be achieved in the future.[16]

With any BCS technique for tumor excision, the aim of the surgeon is to excise the tumor centrally in the specimen. This study reported close margins (≤1 mm) combined with tumor-involved invasive margins, in 42% of cases after NACT, suggesting two out of five patients who underwent BCS had eccentrically located tumors in the lumpectomy specimen. Additionally, despite large volumes, tumor free margins cannot be guaranteed. In palpable and non-palpable tumors without NACT, ultrasound guided BCS result in a reduction of additional therapies compared with other localization techniques.[41,42] Only one study described ultrasound guided surgery (with pre-operatively placed marker) after NACT and concluded that this technique also has the potential to lower tumor-involved margins and resected volume.[43]

One of the limitations of this study is that data is solely based on the pathological findings after BCS for invasive breast cancer and our results do not include further clinical patient or

(pre-treatment) tumor characteristics nor does it include information about additional non-surgical treatment in case of positive margins.
Additionally, despite uniformal guidelines about processing and reporting of biopsies and specimens, pathological reports were incomplete about molecular subtypes. This could be due to determination of molecular subtypes on biopsy after multidisciplinary agreement of performing NACT based on clinical information.

# Conclusion

The primary goal of breast conserving surgery after neoadjuvant chemotherapy, resection of the residual tumor with tumor-free margins, is not accomplished in almost 25%. High risk patients are those with invasive lobular carcinoma or no tumor response after NACT. It is necessary to develop criteria for choosing the type of surgery after NACT and improve visualization of the location and extent of the residual tumor in order to obtain good oncological and cosmetic outcomes.

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